MOLECULAR AND GENETIC MEDICINE AT STANFORD

The program for molecular and genetic medicine, focused in the Center for Molecular and Genetic Medicine (CMGM), defines the academic blueprint for the Stanford School of Medicine in the immediate future—as I suspect it may for many of our comparable peer institutions. The program is designed to maintain and emphasize our uniqueness by recognizing where our exceptional strengths lie.

Stanford's singularity is rooted in the creation and transmission of new knowledge and in facilitating its application to clinical problems. The way we teach, the kinds of students we attract, the strength and elegance of our several MD/PhD programs—for example, our preeminent Medical Scientist Training Program—all contribute to the School's style and environment.

If we begin from that premise and recognize the expanding revolution in the biological sciences, we can anticipate the impact of new molecular insights and tools on the clinical missions of the School of Medicine. The power, the precision, and the applicability of the basic sciences we pursued so vigorously over the past decade have taken quantum leaps and are poised to illuminate our understanding of human health and disease in ways unimaginable only a few years ago.

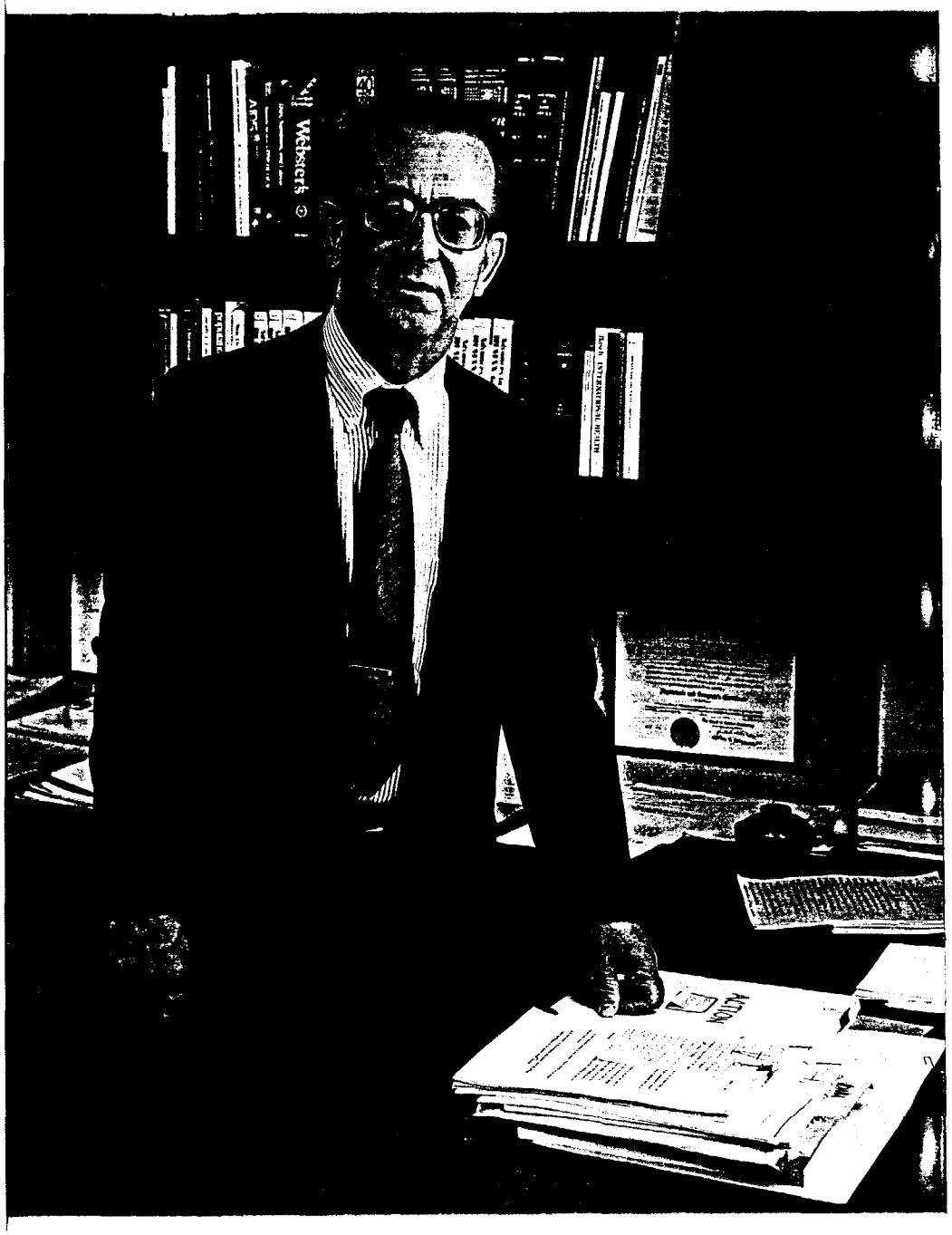
I believe, although my perspective as a pathologist may color my judgment, that the rational practice of medicine must begin with a precise understanding of what is wrong—with a precise diagnosis. Without that knowledge, one must resort to indirect, imperfect analyses and remedies that may be only marginally effective. We now have the capacity to look at diseases in entirely new ways, to gain a more detailed and specific understanding of what has gone wrong, and thus to develop more specific and effective approaches for dealing with these problems.

The purpose of the CMGM and the overarching program is to make it easy for scientifically astute physicians to rub shoulders with clinically astute basic scientists and thus encourage a collision of ideas between the research laboratory and the clinical setting. If we can provide the necessary milieu and context for these interactions, and thereby develop the requisite critical mass, a wonderfully productive synergism will result.

In short, we intend to create a critical mass—the right numbers, the right people, in the right physical and intellectual configurations—then sit back and take pride in the understandings, the insights, the novel therapies and the strategies of disease prevention that will flower from the effort. We expect that this program will also provide an incredible training ground for our students and fellows, predoctorals and postdoctorals, as well as MD/PhD students—that remarkably gifted group of young men and women who are looking for challenging career opportunities in precisely this kind of exciting environment.

From all of this it follows that the Center and the program for molecular and genetic medicine provide for the Stanford medical school exactly the right blueprint by which to shape a remarkable and exhilarating future.

David Korn, MD, Vice-President and Dean, School of Medicine, Stanford University



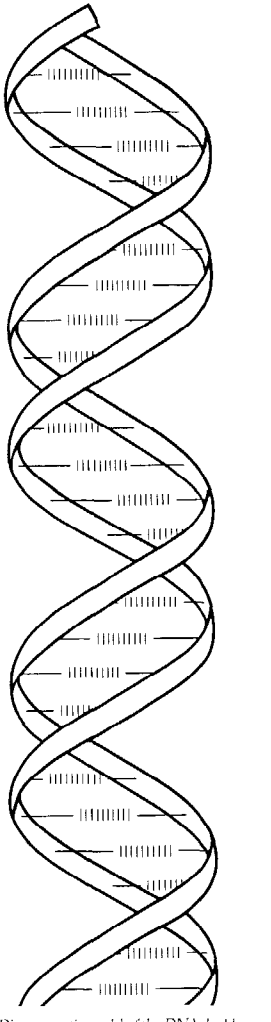
Left: David Korn, MD, was long-time chairman of the Department of Pathology. His research over the past twenty years has focused on understanding the enzymes that are responsible for the replication and repair of DNA in human cells and tissue: DNA polymerases. Dr. Korn is chairman of the National Cancer Advisory Board.

THE NEW BIOLOGY

Questions about the nature of life—how cells grow, reproduce, differentiate, and transmit their characteristics to their offspring—have perplexed mankind for centuries; they have only recently begun to be unraveled through knowledge of DNA (deoxyribonucleic acid). In its double-coiled strands, DNA contains the instructions for every known process of life.

From 1869, when Fredrick Miescher discovered nuclein, biologists, chemists, and geneticists built discovery upon discovery in their search for understanding of the processes controlling heredity. In 1944, three scientists at the Rockefeller Institute—Oswald Avery, Colin McCloud, and Maclyn McCarty—studying the differences between the virulent and nonvirulent strains of pneumococcus, identified deoxyribonucleic acid as the carrier of the genetic code. The culmination of the search for the structure of DNA came in 1953, when James Watson and Francis Crick proposed their double helical model of DNA.

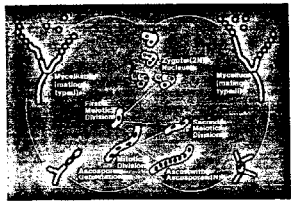
The discovery of the chemical nature of genes and the resultant cracking of the genetic code triggered one of history's most significant scientific revolutions. It led to the present belief that almost all human diseases are, in some way, genetically determined and that given precise understanding of the structure, organization, and regulatory processes of genes, many diseases can be prevented or cured. In the years since 1953, the tools of molecular biology—gene cloning, restriction enzymes, recombinant DNA techniques—have advanced theory to the threshold of practical applications, which offer hope for the prevention, diagnosis, and treatment of human disease.



Diagrammatic model of the DNA double helix (B form).

Edward Lawrie Tatum was a member of the Department of Biology at Stanford from 1937 to 1945, when he went to Yale with the faculty of botany—a year later, microbiology. In 1946, he rejoined biology at Stanford, moving to biochemistry in 1956. In 1957, he left Stanford for an appointment at Rockefeller University.

Tatum and George Wells Beadle, working with Neurospora, hypothesized that each gene specifies an enzyme and thereby facilitates a particular chemical reaction.



Life cycle of Neurospora.

Scientists at Stanford University School of Medicine are poised and equipped to be at the forefront of this new age of medicine through a broadly based, multidisciplinary program in molecular and genetic medicine.

Stanford and the New Medicine

The excitement and promise of the new genetics have deep roots at Stanford, beginning with the appointment of biologist David Starr Jordan, as the university's first president.

The most widely recognized breakthrough of the modern era in genetics came out of the Stanford laboratory of George Beadle and E. L. Tatum. They theorized that each gene specifies an enzyme, and thereby facilitates a particular chemical reaction in a cell (the one-gene-one enzyme hypothesis). In 1958, after both had left Stanford for other academic posts, they shared the Nobel Prize in physiology and medicine with Joshua Lederberg, who was named the following year to head the new Department of Genetics at the medical school.

In that same year, the School of Medicine moved from its hundred-year-old site in San Francisco to the main campus, thereby unifying Stanford's science faculty in one location.

At the same time, the medical school benefited from an infusion of distinguished new faculty: pediatrician Norman Kretchmer from Cornell, Nobel Prize-winning biochemist Arthur Kornberg (along with most of his department) from Washington University, and geneticist Joshua Lederberg from the University of Wisconsin, to join Henry Kaplan in radiology and Avram Goldstein of pharmacology already at the School.

A series of important advances followed. In the 1950s, Rose Payne, then a research associate in medicine, determined the cause of white-cell antibody response following transfusion, leading to knowledge of the human leukocyte antigen (HLA) complex, of major importance to the study of immunology. Later her laboratory played a key role in developing techniques to determine the genetic compatibility of donor and recipient, contributing to the success of organ transplantation at Stanford. From 1963 through 1966, Stanford was a leader in kidney transplantation under the direction of Roy Cohn. In 1969, Norman Shumway initiated the Stanford heart transplantation program, which evolved into heart/lung replacement in 1981.

In the 1960s, building on earlier work at Stanford and elsewhere, Hugh McDevitt discovered a new class of regulatory genes that controls the body's immune response to foreign substances like viruses and bacteria, which suggested that individuals may have predictable genetic susceptibility to certain diseases. About the same time, the world's first device for separating complex cells according to their biological function—the Fluorescence-Activated Cell Sorter (FACS)—was developed in the Department of Genetics and was applied successfully by Leonard Herzenberg to study the body's immune system.

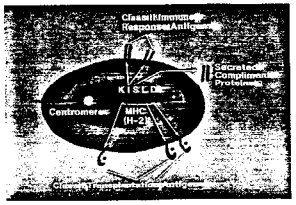
In 1968, David Korn joined Stanford from the National Institutes of Health to head the Department of Pathology. He created a blueprint for the successful melding of distinguished basic science with excellence in clinical practice and teaching.

AN EARLY EXPLORER OF HLA

Rose Payne, emerita professor of medicine, directs the tissue typing laboratory at the Stanford Blood Center. A pioneer in the development of the human leukocyte antigen (HLA) classification system, Payne was among the first scientists to be interested in transfusion reaction in patients who had had multiple transfusions and women who had had several children.

Stimulated by a 1954 paper of Professor Jean Dausset of France, who hypothesized that in certain leukopenias the body produced an antibody to its own white blood cells, Payne began to collect and study sera from patients with low white blood cell counts. She demonstrated that the observed antibodies were the consequence of prior multiple transfusions and the cause of the previously unexplained transfusion reactions, not only in leukopenic patients but any patient who had received many units of blood. She noted that in the absence of prior transfusions, women with several children also developed both these antibodies and transfusion reactions, thus beginning to establish that the woman was immunized by incompatible fetal white blood cell types. By identifying the offending antigens, blood and tissue matching became a reality, opening the door to understanding the HLA complex.

Payne's emphasis then turned to working out a classification for white blood cell types. From then until now, she has disentangled and teased out specific antigens for classification. The Stanford lab tests for eighty tissue types that may be present in thousands of combinations.



Organization of the HMC (H-2 complex) of the mouse.

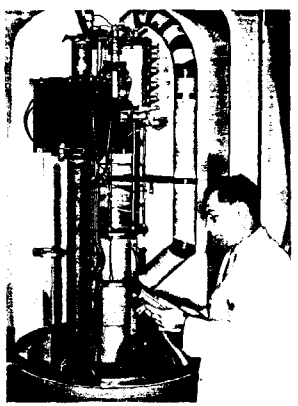
RADIOLOGIST/CANCER BIOLOGIST

Henry Seymour Kaplan, MD, best known perhaps for his development with Stanford physicists of the modified clinical, linear accelerator, achieved a juxtaposition between science and practice that was rare for physicians of his generation.

He came to Stanford in 1948 to head a new Department of Radiology and insisted from the start that radiobiology—the study of the effects of radiation on living biological systems—be pursued. Determined to take on cancer as a life-time adversary (his father developed lung cancer when Henry was only fifteen), he early found that the leukemias and lymphomas interested him most—a decision that strongly influenced the widespread interest in those cancers in many departments at Stanford.

Kaplan's research on mouse leukemia began in an anatomy laboratory at the University of Minnesota, continued at Yale, and led directly to his effective treatment of Hodgkin's disease. In the Cancer Biology Research Laboratory that he headed, his associates carry on the twenty-ninth year of that NIH funding grant.

Before his death in 1984, the Stanford Board of Trustees established the Henry S. Kaplan Professorship in Cancer Biology, the first holder of which will be a part of the CMGM.



Henry Kaplan with Stanford's original linear accelerator in 1955.

The Golden Age of Genetics

In 1971, Paul Berg and his students synthesized the first recombinant DNA molecule from the genes of a tumor virus and the bacterium *E. coli*. A year later, Vittorio Sgaramella, a postdoctoral fellow with Joshua Lederberg in the Department of Genetics, and Ronald Davis and Berg's student Janet Mertz, in the Department of Biochemistry, developed a simple way to join DNA molecules together outside of living cells. In 1973, geneticist Stanley Cohen, then working in the Department of Medicine at Stanford, and biochemist Herbert Boyer at the University of California, San Francisco, collaboratively developed a way to construct biologically functional recombinant DNA molecules and propagate them in living cells, giving rise to the age of genetic engineering. A few years later, Cohen and associates, including Robert Schimke, of the Department of Biological Sciences, showed that mammalian genes could be expressed in bacterial cells.

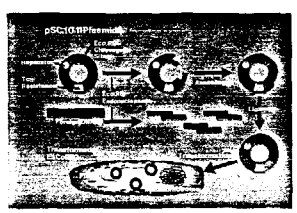
In 1980, Paul Berg was recognized for his "fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant DNA," and brought a second Nobel Prize to the Department of Biochemistry. Over the years, members of the Department—Arthur Kornberg, Robert Lehman, David Hogness, and Dale Kaiser—as well as Stanley Cohen of genetics—had developed novel techniques that allowed researchers to examine the structure and control of genes of higher organisms in previously unimagined ways.

Stanford's contributions in immunology, genetics, biochemistry, and neurosciences in those first twenty-five years were matched by clinical advances that moved from the laboratory to the hospital: heart and heart/lung transplantation; new methods for treating lymphomas, particularly Hodgkin's disease; life-saving techniques, including respiratory therapy, for critically ill newborns; and the use of antivirals and monoclonal antibodies as therapeutic agents. In 1981, Stanley Falkow, a pioneer in the use of genetic engineering to develop vaccines, reorganized the Department of Medical Microbiology. He recruited such outstanding young scientists as John Boothroyd, Edward Mocarski, and Gary Schoolnik for the work, cooperating widely with physicians in the Division of Infectious Diseases. Thomas Merigan, chief of that Division, was an early researcher in the therapeutic use of interferon and is internationally known for his continuing work with antiviral agents. Luigi Cavalli-Sforza, a world-famous population geneticist, has pioneered in the use of DNA markers to trace human evolution and in developing mathematical models for evolution.

A younger generation of talented scientists is working in molecular and genetic medicine at Stanford today. Mark Davis, also of medical microbiology, and associates at the NIH and the University of California, San Diego, have isolated an elusive gene that carries many clues to the immune response. Jeffrey Sklar, pathologist, has developed sensitive new methods of DNA analysis that permit early discovery of cancer cells. James Rothman, biochemist, is studying the role of the Golgi apparatus in protein transport; and Pate Skene, neurobiologist, has discovered a useful growth-associated protein that holds promise for the regeneration of damaged spinal cords.

PIONEER IN GENETIC ENGINEERING

In 1968, geneticist/molecular biologist Stanley N. Cohen, MD, joined Stanford's Department of Medicine and began the study of plasmids—small circular stretches of DNA that are physically separate from the DNA of the bacterial host cell. During these studies, Cohen devised methods for introducing molecules of plasmid DNA into bacteria. From such work came the concept of using the self-replicating plasmids as carriers for the propagation and cloning of foreign genes linked to them. In 1973, he and his associates joined together regions of separate plasmids to yield the first biologically functional DNA molecules constructed outside of living cells. These studies were followed by experiments in which DNA segments from two different bacterial species were linked to form recombinant plasmids that reproduced themselves when reintroduced into cells. Shortly thereafter, Cohen and his associates showed that even DNA derived from animal cells can be propagated in bacteria by linking it to plasmids and that such methods can be used to isolate and study individual genes from complex organisms. In 1978, Cohen—together with Robert Schimke of the Department of Biological Sciences—achieved the first production in bacteria of a biologically active protein encoded by DNA transferred from higher organisms, making practical the construction of bacterial "factories" able to synthesize hormones and other gene products ordinarily made only in animal cells.



Essential features of the DNA-cloning procedure.

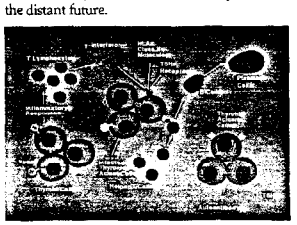
BRIDGING BASIC AND CLINICAL IMMUNOLOGY

Hugh O'Neill McDevitt, MD, was named the 1985 winner of the Lita Annenberg Hazen Award for Excellence in Clinical Research, which cited "his elegant research, which bridges basic and clinical immunology..."

A world leader in studies of genetic control of the immune system and its relationship to disease risk, Dr. McDevitt was a pioneer in uncovering the relationship between the genetic control of the immune response and related susceptibility or resistance to a wide range of diseases such as rheumatoid arthritis, Graves' disease, and insulin-dependent diabetes. He was responsible for many of the crucial discoveries that underlie the association between disease and the human leukocyte antigens (HLA) and for the development of immunological approaches for the treatment of disease. About forty diseases are known to be associated with HLA types that control susceptibility to them.

Some of his findings offer immediate opportunities for patient care; knowledge of genetic susceptibility to a disease may suggest precautionary action. For example, about one in five individuals who carry the B27 marker will develop Reiter's disease secondary to an infection with Salmonella, Shigella, or Yersinia.

Other areas of his research have the potential to prevent autoimmune diseases in the future. In collaboration with Dr. Lawrence Steinman, he has successfully used antibodies produced in the laboratory to suppress in animals a disease similar to multiple sclerosis, but he warns that it is premature to speak of prevention or intervention in autoimmunity in human disease except in the distant future.



The diagram depicts the hypothesized role of HLA class II antigen genes in Graves' disease, which is caused by antibodies to cell-surface receptors for thyroid-stimulating hormone. The antibodies stimulate excess thyroid hormone production (hyperthyroidism). It is not known whether the thyroid acinar cells express their own class II genes

Stanford's Particular Vision

THE CENTER FOR MOLECULAR AND GENETIC MEDICINE

The great discoveries of the past century—antisepsis, vaccination, and antibiosis—eliminated many major killers. The human disorders that remain have been frustrating and difficult to treat because they have been understood imperfectly. Many arise from errors in the development of the fetus: some are so severe that the fetus does not survive; some result in the birth of a deformed child; others remain quiescent until middle-age, when atherosclerosis or kidney disease or cancer occurs. Another broad category involves inappropriate response of the immune system: sometimes too great, sometimes too little. Other diseases ranging from arthritis to alcoholism, from manic depressive psychosis to schizophrenia, have now been identified as genetically destined.

It is unlikely that these diseases will be prevented or cured until their mechanisms are understood—a challenge that calls for scientists and physicians who understand the new biology.

Stanford's program in molecular and genetic medicine grew out of that vision: its purpose to expand and reconfigure the basic sciences, and, at the same time, to build bridges to physician/scientists in clinical departments.

Many clinical departments are already engaged in the study of disease at a molecular level.

A radiation biologist in the Department of Radiology is designing new drugs to enhance the effectiveness of radiation against cancer cells. Psychiatrists are studying the chemicals in the brain that seem to affect mental illness. In a combined effort between immunologists and neurologists, an experimental disease in mice that closely resembles multiple sclerosis is being successfully treated with a genetically engineered protein.

Both the program and the Center in which it is focused are led by Paul Berg, Willson Professor of Biochemistry. The 100,000 square foot laboratory building will house the Department of Biochemistry, the Department of Developmental Biology, the Department of Molecular and Cellular Physiology, and the Howard Hughes Medical Institute Unit in Molecular and Genetic Medicine.

Department of Biochemistry

Biochemistry lies at the heart of the biological sciences and, therefore, at the core of the Center for Molecular and Genetic Medicine. Stanford's Department of Biochemistry is internationally recognized for its research in the fields of genetic chemistry and cell biology. Its alumni, numbering in the hundreds, include many of the leaders of contemporary molecular and cell biology. Initially organized and led by Nobel laureate Arthur Kornberg, the nine faculty members include a second Nobel laureate, Paul Berg, and seven members of the National Academy of Sciences. The Department's work in biochemistry, molecular genetics, and the related fields of protein structure and function will be fundamental to all groups in the Center and in the training of physician/scientists at Stanford.

The Department's research in the 1960s, inspired by interest in the mechanisms and regulation of DNA replication, recombination, and repair, and later by the expression and control of genetic information, laid the foundation for the recombinant DNA breakthrough in the early 1970s. The concomitant development of molecular cloning by geneticist Stanley Cohen and his colleagues paved

RESEARCH: THE LIFELINE OF MEDICINE
Arthur Kornberg, MD

When several of us came together to Stanford from St. Louis in 1959 to form a new Department of Biochemistry, we believed that biochemistry was the keystone of medical education and practice. We still do.

The Department has since played an important role in the revolutionary development of knowledge about DNA, an effort that everyone in the Department has contributed to significantly. And yet, our research was not designed for practical application, and none of us anticipated that the work on DNA would lead to major applications in medicine and industry.

All the thunder and excitement generated from the application of recombinant DNA technology to the problems of human disease points to an even greater need for emphasis on basic scientific inquiry. For instance, recent studies on the manipulation of DNA have shown that the work will progress only through increased knowledge of the proteins involved in carrying out and controlling DNA synthesis and the expression of its genetic content. The people who are working on these proteins have not had adequate recognition and support—a state that must be corrected if we are to solve basic problems in biology and medicine.

Many times I have described basic research as the "lifeline of medicine." Research is essential for advances in medicine: there will be no solutions to major disease problems for which we lack basic knowledge, short of acquiring that knowledge. In speaking to physicians at professional meetings over the years, I have expressed my belief that they—we—have not fully enjoyed and expressed our creativity in applying science to everyday medical questions.

The Stanford Center for Molecular and Genetic Medicine, with the Department of Biochemistry as an integral part, will encourage generations of young physicians to share the vision of what the science of medicine can and will be in the future.

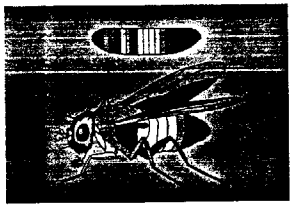


Diagram of the egg of the fruit fly Drosophila *and an adult fly, showing where genetic features identified in the egg appear in the adult's body. (David Hogness)*

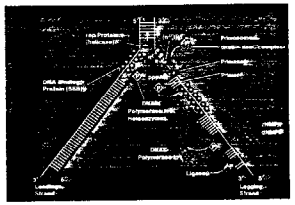
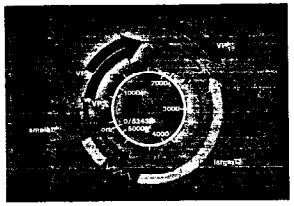
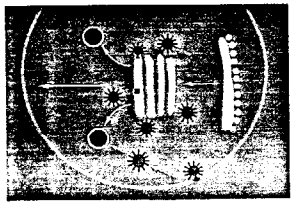


Diagram shows how enzymes operate in the replication of the DNA of a bacterial chromosome. (Arthur Kornberg)



SV 40 Genome. (Paul Berg)



The Golgi stack distributes proteins that have just been made in the endoplasmic reticulum (ER) to their final destinations in the cell. These include the cell surface plasma membrane (PM), secretion granules (SG), and lysosomes (LYS). (James Rothman)

the way for the explosive impact of molecular biology in medicine, industry, and agriculture.

The principal research focus has been and continues to be concerned with the structure and function of macromolecules—DNA, RNA, and proteins—in both higher and lower organisms. Recently, these fundamental interests have expanded to include the developmental controls that determine the body structure of the fruit fly, the ways certain bacteria alter their growth cycles, and the mechanisms by which the newly synthesized proteins are targeted to specific cellular locations.

The Arnold and Mabel Beckman Laboratories for Biochemistry, in the Center for Molecular and Genetic Medicine, were funded by a gift from the Arnold and Mabel Beckman Foundation.

Department of Developmental Biology

How a single, fertilized egg develops into a multicellular adult animal has been a fundamental question of biology for many years. As cells within the egg divide and differentiate, the body plan begins to emerge, and a complex set of cell movements, cell interactions, microenvironments, and sequential activation of genes results in an intact and functioning organism.

For many years, developmental biology was essentially a study of embryology; during the past decade, that focus changed dramatically. Advances at the molecular level, particularly the genetic control of development, have been explosive, yet they are only the beginning of a major movement throughout biology to understand the mechanisms underlying developmental decisions in the

cell and the effect of those decisions on cell structure and function.

The new Department of Developmental Biology will interact closely with others in the Center: with biochemistry's interest in control of gene expression, chromosomal replication, and protein transport within the cell; with physiology because of the latter's planned focus on cell-to-cell communication; with the Unit in Genetic Medicine through that group's interest in oncogenes and their role in development.

Developmental biology will also have important ties outside the Center: with faculty studying the development of the immune system in mammals (genetics, medical microbiology, medicine, and pathology); with the Department of Biological Sciences on questions of plant and animal development. Fundamental discoveries in developmental biology can be rapidly transferred to physicians in the Departments of Pediatrics, Medicine, and Gynecology/Obstetrics and thereby aid in averting errors in the development of the fetus.

Department of Molecular and Cellular Physiology

There could scarcely be a more stimulating time for physiology than the present, as major problems posed by organ physiology—heart and lung disease, diabetes, and growth regulation—are being solved in the language of cellular and molecular biology.

The new Department will investigate the gene products that regulate cells in important physiological systems: the machinery that governs their properties, messages, responses, interactions, and functions. As such, the work will have a major and important impact on medical therapeutics—the endocrinology, metabolic medicine, and

THE DEVELOPMENTAL BIOLOGY OF THE IMMUNE SYSTEM

Irving Weissman, MD, professor of pathology, has studied the immune system for twenty years with a series of fundamental discoveries to his credit: how cells in the system develop, how they recognize and remove foreign substances, how they migrate to where they are needed, and how certain lymphatic cancers may arise. While he has worked for many years on the development of T lymphocytes, his most recent work involves, in addition, the developmental biology of B cells.

Since there is no way to predict where an infection will attack, specialized organs—spleen, Peyer's patches, and lymph nodes—collect the foreign substances from wherever they enter. To get the right lymphocyte in the right place at the right time, most lymphocytes are mobile and acquire molecules (homing receptors) that allow them to traffic from one part of the body to another, stopping at a site that has a matching antigen receptor. Weissman's group has discovered that there are at least two homing receptors on most lymphocytes: one that will go to any lymph node; one that goes only to a gut-associated structure—the Peyer patch. Most tumor cells (leukemias and lymphomas) have only one or the other homing receptor.

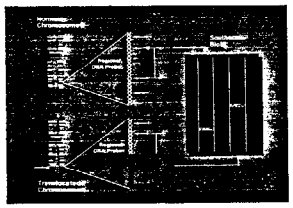
One way to study the developmental biology of lymphocytes is to ask when the homing receptors develop then work back from that point using clones as a tool.

The group has succeeded in isolating and purifying pluripotent stem cells from the bone marrow and is now asking, at the single-cell level, at what stage a developmental commitment is made. Weissman asks, "Can we take this body of cells and prove that they are homogeneous and will respond to the different microenvironments in which they mature? Or are they already developmentally committed and heterogeneous?" It is a fundamental question whether one is studying the fly, the mouse, or a human liver. The answer has great clinical significance for bone marrow transplantation and, by using the homing receptors, for predicting tumor metastasis.

A PAIR OF CANCER RESEARCHERS

The names of oncologist/immunologist Ronald Levy and pathologist Jeffrey Sklar have been joined recently in journal articles involving B-cell lymphomas. Dr. Sklar has focused on the identification of lymphomas, Dr. Levy on individually designed therapies.

Jeffrey Sklar, MD, PhD, has developed powerful molecular tools to detect and characterize cancer in patients: a "fingerprinting method"—immunogenotyping—which distinguishes quickly and accurately between benign and malignant processes of lymphocytes; and molecular hybridization probes to detect chromosomal changes that are consistent and specific in certain cancers.



A DNA hybridization probe diagnoses chromosomal changes associated with cancer by detecting changes in position of bands in Southern blot autoradiogram.

Ronald Levy, MD, directs the Armand Hammer Cancer Research Laboratory, where he has worked in developing monoclonal antibodies for diagnosis and treatment of cancer. He was the first physician to report success in treating a cancer patient with monoclonal antibodies. He is now assessing strategies that combine tailored therapeutic antibodies with enhanced immune response by patients to their own tumors.

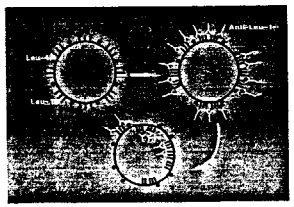


Diagram shows monoclonal antibodies reacting to antigens on the surface of tumor cells. Following response, antigens are swept off the surface of the cells in a process called antigenic modulation.

allergy medicine of the future.

One question concerns the way intercellular messages are packaged and sent and how they are recognized and received by target cells. The distribution of cholesterol and fats throughout the body via a messenger system of blood lipoproteins is one such system. Disorders in the production of this lipoprotein packet, in the handling of the packet in the blood, and in the receptor system can lead to heart disease, atherosclerosis, and stroke.

The brain and its associated pituitary gland are another example of intersystem communication. They instruct several organ systems by hormones whose synthesis and regulation are genetically encoded. The list of diseases involving the inappropriate sending and reception of these small molecule messages would include much of what is called endocrinology today. These systems also have important consequences in pediatric and geriatric medicine.

Two examples involve the immune system's response to offending agents and the blood vascular system's reaction to infection. A network for sending and receiving these messages extends throughout the body, but the study of how the messages are formed and sent and how they are received by other cells has only begun. Full understanding of these mechanisms should greatly improve the treatment of shock, allergy, infectious diseases, and hypertension.

The Howard Hughes Medical Institute Unit in Molecular and Genetic Medicine

The Unit in Molecular and Genetic Medicine is expected to be the lynch pin that links basic scientists with clinical scientists. It will be

responsible for speeding the transfer of basic information into clinical science and vice versa by determining what questions about gene organization and regulation are relevant to understanding diseases uncovered by or being treated by clinical scientists.

The Unit will be concerned primarily with questions of gene structure, organization, and regulation in genetically based diseases. Its research is likely to provide the basis for the mapping of genetic diseases to particular locations on a chromosome and for learning how rearrangements or mutations of chromosomes occur and cause disease; the development of rapid, precise, and efficient diagnostic tests for known genetic diseases; and the development of therapy based on gene or cell replacement. The bone marrow will probably be the first vehicle for gene therapy because of the substantial experience physicians have had over the past decade in bone marrow transplantation in the treatment of blood cancers, anemias, and congenital immune deficiencies.

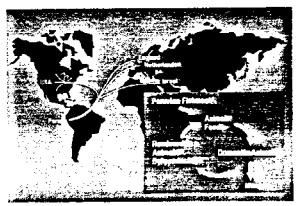
The Unit in Molecular and Genetic Medicine is expected to be particularly important in the training of a new generation of scientist/physicians who will work at the interface of medicine and molecular biology. The laboratories that will make up the Unit have been funded by the Howard Hughes Medical Institute.

A BIOMEDICAL BRIDGE TO THE THIRD WORLD

Gary Schoolnik, MD, is assistant professor of medicine and medical microbiology, chief of the Infectious Disease Service at the VA medical center, and heads a new Division of Geographic Medicine.

He and his colleagues in the Division believe that their work can build a bridge between the advanced biotechnology of the West and the medical needs of Third World countries. "We take a special interest in these problems" he says, "because of the significance of these infections for the health of millions of the world's peoples; because of the emerging geopolitical importance of these countries; and because molecular biology has made it possible to create new reagents for the diagnosis, prevention, and therapy of these diseases. Moreover, it is a matter of simple ethics, in my view, for an affluent country and a preeminent university to focus their expertise and resources on the needs of less fortunate peoples."

Dr. Schoolnik's laboratory has been working with a group of pathogens that are widespread and virulent in developing countries: three bacterial species that cause serious infectious diarrhea; human papilloma virus, which is associated with cervical carcinoma, the second most common cancer of women in the Third World; and gonorrhea, which has resulted in an epidemic of infertility in Western Africa. In each instance, the investigators have pursued a similar strategy: to identify the microbe's virulence determinants; to determine their structure at the molecular level; and to design new anti-infectives using techniques of molecular biology.



An international epidemic of Salmonella agona *infections in man and animals traced to Peruvian fishmeal, 1969-72.*

THE MEDICAL SCIENTIST TRAINING PROGRAM

David Clayton, PhD, has directed Stanford's Medical Scientist Training Program since 1977. This combined MD/PhD graduate program is funded by the NIH and currently enrolls 40 trainees. The majority elect to pursue their PhD thesis in a basic science department of the medical school, although a significant number have trained in biomedical research laboratories in clinical departments or interdepartmental programs. Students in this program are committed to a career at the interface between contemporary biology and clinical medicine. It would be logical for this program to be a core element of graduate training in the CMGM.

Dr. Clayton, of the Department of Pathology, has focused his research interests on the structure, mode of replication and transcription, and genetic content of mammalian mitochondrial DNA. His laboratory obtained the entire nucleotide sequence of mammalian mitochondrial DNA in 1981 and now centers on defining the molecular mechanism of genetic expression of this organelle DNA and how nuclear genes control organelle biogensis.

David Clayton is associate director of CMGM.

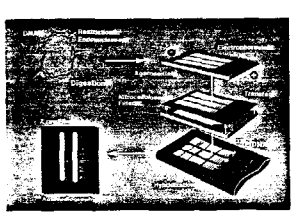


Illustration of the technique used for Southern blotting. Radioactive DNA probes are used to detect specific DNA fragments produced by restriction enzyme digestion of toral genome DNA. This tool has been instrumental in the development of gene cloning, transcription analysis, and gene mapping. (Thomas Reynolds)

LINKAGES FROM CENTER TO PROGRAM

One of the principal goals of the Center is to encourage and nourish interaction among these four units. Using broad strokes, that interaction might be described this way: *Biochemistry* is the wellspring that supplies the molecular design of how genes control structure. Drawing from that design, *developmental biology* focuses on the processes that guide one cell to produce complex organisms and the genetic regulation of that process. *Cell physiology* asks how cells are assembled, how they send and receive messages, and how they are integrated into important physiologic systems. Finally, the *Unit in Molecular and Genetic Medicine* explores the problems of human disease, using the tools and information that comprise molecular and cell biology.

Although not housed in the Center, basic scientists in the Departments of Genetics, Pathology, Medical Microbiology, and Medicine will participate in the ongoing programs of the Center. Similarly, physicians from the clinical Departments of Medicine, Pediatrics, Pathology, and Gynecology/Obstetrics, whose interests and activities center on human genetic disease, will form a bridging unit outside the center in clinical genetics.

By providing new laboratories, construction of the Center permits the School to add distinguished faculty members to complement the present professoriate. About half of the faculty investigators who will occupy the Center will, in fact, be newly recruited. Search and academic planning committees are working to identify and recruit the leadership for the new units and they, in turn, will set the academic direction and recruit other faculty for the new groups.

In planning the CMGM, graduate education has been seen as one of its most critical and promising aspects. Consequently, graduate and postdoctoral training programs that will accommodate up to one hundred graduate students and nearly three times that number of postdoctoral fellows have assumed a high priority in the planning efforts. A successful biomedical research training program should provide the kind of broad opportunity that is foreseen for the Center. The presence of world leaders in the many disciplines represented at Stanford should be a lodestone in attracting the best of the next generations of scientists.

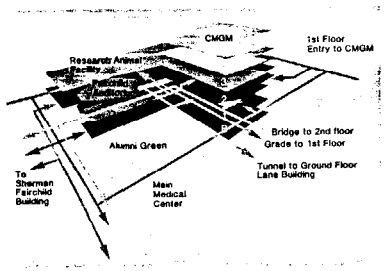
Left to right: David Clayton with four MSTP students: Thomas Reynolds, a fifth-year student who works in the laboratories of pathologists Jeffrey Sklar and Roger Warnke; David Chang, a fifth-year student in biophysics, who works in Clayton's laboratory; Alan Sachs, a Cornell graduate and fourth-year student whose research takes place in the Department of Cell Biology; and Catherine Berlot, who attended Princeton University and now works in James Spudich's laboratory in cell biology. She is a fifth-year student.

Electron micrograph of a unicircular dimeric mammalian mitochondrial DNA molecule. This genome contains two displacement loops at the two diametrically opposed origins of DNA replication. Copying of the genetic information in mitochondrial DNA also begins at these loops. (David Chang)

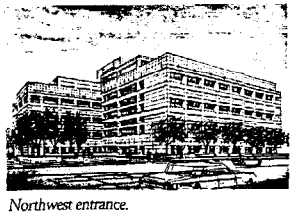
The poly (A) tail of messenger RNA may play a role in the regulation of messenger RNA transport and degradation in the yeast cell. (Alan Sachs)

Stimulation of Dictyostelium amoebae with the chemoattractant cAMP results in transient increases in myosin phosphorylation, which coincides with chemotactic movements. Changes in myosin phosphorylation have been shown to alter myosin motility and assembly state. A scanning electron micrograph from Cooke et al (1976).

THE BUILDING



Fourth floor: Department of Biochemistry.
Third floor: Department of Developmental Biology plus shared resources with the Department of Biochemistry.
Second floor: Howard Hughes Medical Institute Unit in Molecular and Genetic Medicine.
First floor: Department of Molecular and Cellular Physiology plus elements of the Unit in Molecular and Genetic Medicine.
Ground floor: 100-seat lecture hall; core laboratory support facilities (e.g., cell sorter, fermentation unit, DNA and protein synthesizers); director's offices; research commons; machine and electrical shops.



Northwest entrance.

Southwest perspective.

The Stanford Center for Molecular and Genetic Medicine represents a major commitment to bridge the basic sciences and clinical application. The Center will accommodate nearly forty faculty members with their graduate students and research teams. Its five levels will provide about 100,000 square feet of laboratory and office space adjacent to the Sherman Fairchild science complex, the Research Animal Facility, and the core buildings of the School of Medicine. It will be joined at three levels to the science complex and the animal buildings. The Stanford University Hospital and the Children's Hospital at Stanford are nearby.

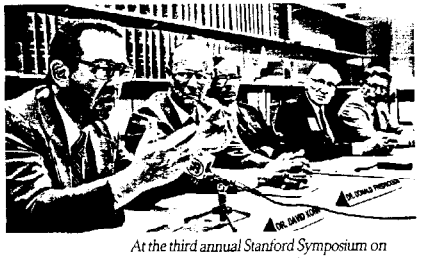
The architects (MBT Associates of San Francisco) have worked closely with a faculty committee to design a visually pleasant building that meets the needs of today's science and instrumentation.

The two largest programs—the Department of Biochemistry and the Unit for Molecular and Genetic Medicine—will each occupy a full floor plus shared resources on the floor below. Biochemistry and developmental biology will be side by side; molecular and genetic medicine will share a floor with physiology. A central core of elevators and an attractive open stairway, complemented by open, well-lighted staircases at the corners, should ensure fast and easy vertical movement of people between floors.

Four- and six-person laboratories will form the perimeter of the four above-grade levels with faculty offices opening into the laboratories, so the investigator is part of the experimental activity. Each floor will also have a core of common space: laboratory support; a conference/library/lounge area; a pantry, copy rooms, and office services. The ground floor will hold a 100-person lecture hall, a dining commons, specialized instrumentation facilities, electrical and machine shops, and administrative offices. Design is under way, with construction scheduled to begin in summer 1986 and completion two years later. The building will cost nearly $50 million and will be funded entirely by gifts.

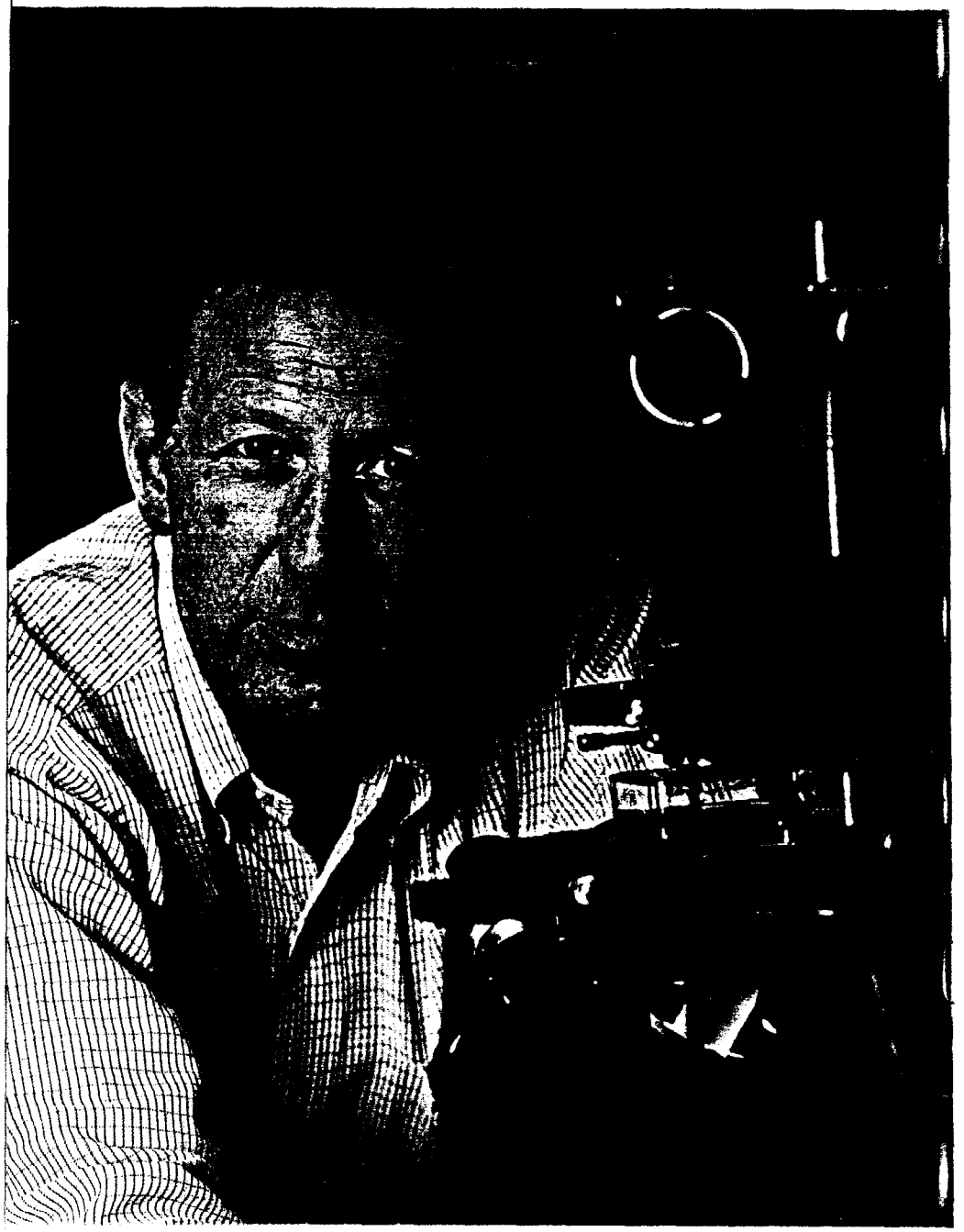
The founding contributors—the Howard Hughes Medical Institute, the Arnold and Mabel Beckman Foundation, and the Lucille P. Markey Charitable Trust—will be joined by other philanthropic individuals and foundations. Gifts will support construction of the building and related research programs to be carried on by faculty and student research groups.

Funds from the Howard Hughes Medical Institute and the Beckman Foundation contributed to the building; the Markey Trust established the new Department of Developmental Biology.



At the third annual Stanford Symposium on Molecular and Genetic Medicine, in May 1985, President Donald Kennedy announced commitments of nearly $30 million to the Center: a $12 million gift from the Arnold and Mabel Beckman Foundation; and $17 million in advanced lease payments from the Howard Hughes Medical Institute. The photograph shows (left to right): David Korn, dean; Donald Fredrickson, president of the Howard Hughes Medical Institute; Arnold Beckman; and Paul Berg.

Uta Francke, of the Department of Human Genetics at Yale School of Medicine, addressed a Stanford audience at the Beckman Scientific Symposium on Genes and Disease in September 1985.



Left: Paul Berg, PhD, was awarded the Nobel Prize for chemistry in 1980. He holds the Jack, Lulu, and Sam Willson Professorship in Biochemistry.

CONCLUSION

Recent advances in biology have triggered a revolution, perhaps the most profound intellectual revolution of our time. The logic of life, its origin and evolutionary history, stand revealed in each organism's genes. Now, many of the conjectures concerning the extraordinary diversity and relatedness of living forms are informed by precise information on the molecular structure, expression, and regulation of genes.

Once as inaccessible and mysterious as the material of the galaxies, genes are now readily obtainable in pure form and in virtually unlimited quantities for chemical analysis and modification. This achievement has radically altered our perspective on health and disease. Indeed, most—perhaps *all*—human disease results from inappropriate gene structures that alter or prevent normal function. These discoveries and the promise of others to come have profound implications for the future of medicine, for they have placed us at the threshold of new methods of diagnosis, prevention, and treatment of human disease.

Stanford's commitment to the establishment of a Center for Molecular and Genetic Medicine is innovative and bold and thereby honors Stanford's pioneering traditions in science and medicine. Moreover, the expansion of our efforts in molecular, cellular, and developmental biology builds on the strengths of an already distinguished faculty and teaching programs in these areas of research. But placing that growth in the midst of existing and newly recruited scientist/physicians, physician/scientists, and their students will speed the exchange of discoveries and new technologies between the laboratory and the clinic. Bridging the discovery gap between basic science and clinical medicine is the keystone for building the "new medicine."

Having been an early participant in fomenting the current biological revolution, it is my privilege to lead the explorations of its applicability to the needs of medicine. Our success in mounting this ambitious venture and the prospects for making it a reality owe much to the encouragement and financial support of several founding organizations and individuals who share that vision.

Paul Berg, PhD, Director, Center for Molecular and Genetic Medicine

Center for Molecular and Genetic Medicine
School of Medicine, Stanford University
Stanford, California 94305

Computer graphics, courtesy: Medical Graphics, Visual Art Services, Stanford University Medical Center: pages 10, 12; Information Graphics, Information Technology Services, Stanford University: pages 4, 5, 7, 8, 10, 13, 15, 16.

Photographs: pages 2, 15, Timothy Holt; pages 4, 6, Stanford News and Publication Service; page 17 (top), Edward Souza, (bottom), Robert Isaacs; page 18, Steve Northrup.

DNA diagram, page 3, courtesy Arthur Kornberg and Charlene Levering. From *DNA Replication* (1980).

Diagram page 8, redrawn and reproduced with permission, *Hospital Practice*. "The HLA System and its Relation to Disease." by Hugh